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Kupper, N.; Denollet, J.

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Explaining heterogeneity in the predictive value of Type D personality for cardiac events and mortality

Nina Kupper *, Johan Denollet

CoRPS - Center of Research on Psychology in Somatic diseases, Tilburg University, The Netherlands

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ABSTRACT

Background: Type D personality has been associated with adverse outcomes in patients with coronary artery disease (CAD). However, large heterogeneity exists between Type D studies, including some studies reporting null-findings.
Objectives: The aim of this study was to examine i) choice of endpoint and ii) age as two study characteristics that may partly explain this large heterogeneity in the Type D associated prognostic effect.
Methods: We used four existing data cohorts of 1503 CAD patients (89% male, mean age = 57.2 ± 9.1) with baseline measures of Type D and endpoints >5 years follow-up: *major adverse cardiac events* (*MACE*), *cardiac death/MI*, and *non-cardiac death*. Patients were classified in 4 age categories: <50 y, 50–59 y, 60–69 y and ≥70 y. Multiple logistic regression models included age, sex, and clinical covariates.
Results: At follow-up, there were 295 events, including 116 cardiac death/MI, and 37 non-cardiac deaths. Both continuous and categorical measures of Type D predicted adverse events. Type D was independently associated with MACE (OR = 1.82; 95%CI 1.33–2.50) and cardiac death/MI (OR = 2.49; 95%CI 1.55–3.99). However, Type D was not associated with non-cardiac death (OR = 1.23; 95%CI 0.57–2.69). Regarding age, Type D consistently predicted MACE in the lower age groups (all ORs ≥ 2.20, all *ps* ≤ .004), but not in patients aged ≥70 y (OR = 1.43, p = .57).
Conclusions: Choice of endpoint and age modulated the risk conferred by Type D personality. Type D was associated with an increased risk of cardiac events, but not with non-cardiac death, or with events in patients aged ≥70 y. Research on psychosocial risk in CAD should account for different sources of heterogeneity in study characteristics.

1. Introduction

Cardiovascular disease is a leading cause of death in the Western world, with coronary artery disease (CAD) being the major culprit. Even though mortality rates have dropped significantly over the past decade, owing to improved treatment and reduced post-infarction mortality, it is important to even further reduce this event rate [1]. Besides classical risk factors, psychological factors such as emotional distress have emerged as potent risk factors as well. In addition to depression [2], other psychosocial factors such as anxiety [3] and personality traits [4,5] have also shown to be important in risk stratification for CAD prognosis. A fairly large body of research has examined the association of Type D personality (i.e. the general tendency towards emotional distress characterized by high scores on social inhibition and negative affectivity traits) with prognosis in patients with cardiovascular disease [6].

Several recent meta-analyses [7–9] have indicated that Type D is associated with an approximately doubled risk of adverse events and mortality, predominantly in patients with coronary artery disease (CAD). However, these meta-analyses reported large heterogeneity between studies [7–9], and negative findings have been reported in Type D studies that used all-cause mortality as an endpoint in patients with CAD [10] and heart failure [11–13]. Therefore, a better understanding of when and how Type D influences cardiovascular prognosis and other adverse outcomes is needed to explain the observed heterogeneity in studies [7], and mixed findings regarding prognosis [14].

Most human illnesses, CAD alike, are etiologically complex, with multiple interacting factors influencing illness incidence and prognosis [15]. These factors may also alter the effect of psychosocial risk markers, such as Type D, in different subgroups. To avoid spurious findings, subgroup analyses need to be pre-specified, and based on theory and biobehavioral disease processes [16]. Heterogeneity analysis in the most recent meta-analysis showed that disease stage (CAD vs. heart failure) was one source of heterogeneity [7]. There are at least two other factors that may explain part of the heterogeneity observed in the prognostic effects of Type D personality, i.e., the choice of endpoint and age.

* Corresponding author at: Department of Medical and Clinical Psychology, Tilburg University, P.O. Box 90153, 5000 LE Tilburg, The Netherlands.
E-mail address: h.m.kupper@tilburguniversity.edu (N. Kupper).

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The choice of endpoint is a crucial determinant of the prognostic effect of a risk factor [17]. While Type D studies reporting null findings focused on all-cause mortality [10–13], positive studies also used cardiac endpoints [7], suggesting that Type D may be more related to fatal and non-fatal cardiac events [14]. Others showed that social avoidance (a trait that is closely related to Type D) predicted cardiac death but not non-cardiac death [18]. The age composition of the sample is another potential effect modifier, and thus a potential explanation for heterogeneity in findings. The risk of adverse events is already higher in older patients due to an aging heart [19–21], and older age is included in the Euroscore-II and Framingham risk scores. Preliminary data showed that the adverse effect of Type D was more pronounced in younger than in older patients [22], suggesting that the risk conferred by Type D may change with age. Moreover, age-associated conditions, such as kidney disease, anemia, frailty, and cognitive dysfunction, have prognostic impact, explaining a substantial part of the variance in mortality risk in the relatively older age groups [23]. Therefore, the current individual patient-based re-examination of four consecutive cohorts of CAD patients [24–27] will examine whether choice of endpoint and age can explain heterogeneity in the prognostic effect of Type D personality.

2. Methods

2.1. Patients

This paper reports on 1503 patients with CAD (89% men; mean age: 57.2 ± 9.1 years) from the Antwerp cardiac rehabilitation program who were enrolled during 4 consecutive primary studies: 303 patients in the 1st cohort (1985–88) [24], 322 in the 2nd cohort (1989–92) [25], 337 in the 3rd cohort (1993–97) [26] and 541 in the 4th cohort (1998–2005) [27]. Methodological details have been described previously [24–27]. At baseline, patients provided written informed consent and completed personality measures. Patients with other major conditions (e.g., cancer) were excluded. This study was approved by the Medical Ethics Committee of the University Hospital Antwerp (protocol 5/48/193).

2.2. Type D personality

Social inhibition and negative affectivity were assessed in each cohort [24–27], with slight differences between cohorts. In the first cohort, the inhibition scale of the Heart Patients Psychological Questionnaire (HPPQ) and the State-Trait Anxiety Inventory (STAI) were used [24], while the DS-16, developed based on previously mentioned questionnaires, (Cohort 2 & 3; [28]) and DS14 (Cohort 4; [29]) were used in subsequent cohorts. The use of different measures was unrelated to Type D prevalence rates ($p = 0.54$) and did not alter associations with adverse events across the 4 cohorts ($p = 0.55$), which justified the pooling of data across Type D measures used in the different cohorts.

Type D can be assessed as a continuous (negative affectivity x social inhibition interaction) or categorical (categories based on high/low trait levels) variable [27,30]. Social inhibition and negative affectivity scores of these measures were transformed to standardized ***Z*** scores (mean = 0; standard deviation = 1) in analyses using continuous measures of Type D. As there are arguments in favor of both approaches, we used both to examine the prognostic value of Type D. For the categorical analyses, previously published cut-off scores on negative affectivity and social inhibition scales [24,28,29] were used to construct 4 groups: a) *low* negative affectivity/*low* inhibition, b) *low* negative affectivity/*high* inhibition, c) *high* negative affectivity/*low* inhibition and d) *high* negative affectivity/*high* inhibition.

2.3. End points

The follow-up interval was on average 8 years in the 1st cohort [24] and 5 years in the subsequent cohorts [24–26]. Information on mortality, nonfatal MI and CABG/PCI was extracted from hospital records and the patient's attending physician was involved in the classification of cause of death. Survival status was confirmed through telephone contact with all participants or their families. We used three endpoints. The first end point was major adverse cardiac events (MACE; a composite of death, MI, CABG, PCI or progression of CAD as documented by angiography). The second end point was cardiac death or MI as a rigorous measure of cardiac prognosis. Finally, we examined the association with non-cardiac death, which was defined as all other, non-cardiac, natural causes of death.

2.4. Subgroup analyses

We examined the effect of Type D in two pre-specified subgroup analyses that were based on i) choice of endpoint (as described above) and ii) age. With respect to age, we made four subgroups, representing patients aged below 50 years (n = 299), between 50–59 years (n = 569), between 60–69 years (n = 522) and 70 years or older (n = 113), inspired by the potentially differential etiology and prognostic risks associated with the younger and older age groups [19–22].

2.5. Covariates

The covariates that proved to be significantly related to adverse events in the four original reports [24–27] were used in the current analysis, including age, sex, index MI, and CABG/PCI at baseline, left ventricular ejection fraction (LVEF) [31] and physical fitness [32]. Poor physical fitness was defined by a median split for peak work load on an exercise test (≤140 and ≤120 W for men aged ≤55 y/≥56 y; ≤100 and ≤80 W for women aged ≤55 y/≥56 y) [25].

2.6. Statistical analyses

Because the older cohorts [24,25] may differ medically due to advancements in medical treatment, we first compared patients that were enrolled between 1985–1994 ($N = 742$) and between 1995–2005 ($N = 761$) to examine any differences in end points, covariates and Type D personality traits. For this purpose, we used Pearson chi square tests for categorical variables and Student t-tests for continuous variables.

Three hierarchical multiple logistic regressions were performed to assess the association of Type D personality with MACE, cardiac death/MI, and non-cardiac death as separate end points We performed these analyses twice, once for the continuous Type D measure (interaction of NA and SI z sores) adjusting for the main NA and SI effects [30], and once for the categorized Type D measure in which the low NA/lowSI category was used as a reference.

To examine the age effects, for each age subgroup, hierarchical multiple logistic regressions were performed with MACE (including cardiac death) as outcome variable. In all regression models, Type D variables were entered together with a priori defined covariates. SPSS 19 (IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY) was used for all analyses and a p value of .05 was considered significant.

3. Results

3.1. Adverse events

There were 295 patients who experienced an adverse event, including 93 deaths. All deaths were attributable to natural causes, of which 56 were considered cardiac deaths and 37 non-cardiac deaths (18 due to cancer and 19 due to other natural causes). Non-fatal events included (recurrent) non-fatal MI ($n = 60$), CABG ($n = 44$), PCI ($n = 120$), and CAD progression on angiography ($n = 12$).

Table 1
Sample characteristics for total sample, and stratified by sample cohort.

	Total (N = 1503)	1985–1994 cohort (*N* = 742)	1995-2005 cohort (*N* = 761)	P value
Demographics				
Age *Mean ± SD*	57.2 ± 9.1	56.0 ± 7.9	58.3 ± 9.9	<.0001
Male sex	1334 (89%)	669 (90%)	665 (87%)	.088
Clinical variables				
Index MI at baseline	731 (49%)	390 (53%)	341 (45%)	.003
CABG at baseline	820 (55%)	450 (61%)	370 (49%)	<.0001
PCI at baseline	415 (28%)	107 (14%)	308 (41%)	<.0001
Decreased LVEF (<50%)	332 (22%)	131 (18%)	201 (26%)	<.0001
Poor exercise tolerance*	555 (37%)	244 (33%)	311 (41%)	.001
Medication use				
Aspirin	1228 (82%)	551 (74%)	677 (89%)	<.0001
Beta-blocker†	966 (65%)	395 (53%)	571 (76%)	<.0001
ACE inhibitor/ARB†	387 (26%)	68 (9%)	319 (43%)	<.0001
Personality				
High NA only	242 (16%)	119 (16%)	123 (16%)	.95
High SI only	303 (20%)	162 (22%)	141 (19%)	.11
Type D personality	451 (30%)	223 (30%)	228 (30%)	.97
Adverse events				
MACE	295 (19%)	150 (20%)	145 (19%)	.57
Cardiac death/MI	116 (8%)	59 (8%)	57 (8%)	.74
Non-cardiac death	37 (2.5%)	18 (2.4%)	19 (2.5%)	.93

Numbers are presented as N (%) unless otherwise indicated. CABG = coronary artery bypass surgery; MACE = major adverse cardiac event; MI = myocardial infarction; PCI = percutaneous coronary intervention.
*≤140/≤120 W for men; ≤100/≤80 W for women; † N = 1489

3.2. Cohort effects

Comparing the cohorts of patients recruited in 1985–1994 (n = 742) and in 1995–2005 (n = 761) showed that the prevalence of Type D personality was 30% in both cohorts (Table 1). With respect to treatment, there were large differences, as could be expected, due to medical advancements over the past 30 years. There was a decrease in CABG, and an increase in PCI, aspirin, beta blocker, and ACE-inhibitor use. However, the interaction between Type D and cohort (1985–1994 vs 1995–2005) was not significant in the prediction of MACE (OR = 0.78; 95%CI 0.046–1.32, p = .35), indicating that cohort-related changes in cardiac treatment did not alter the association of Type D with adverse events. Type D was associated with an increased risk of MACE ($OR_{cohort\ 1}$ = 2.60; 95%CI 1.80–3.77; $OR_{cohort\ 2}$ = 2.03; 95%CI 1.39–2.94), and cardiac death/MI ($OR_{cohort\ 1}$ = 3.56; 95%CI 2.07–6.12 and $OR_{cohort\ 2}$ = 2.63; 95%CI 1.53–4.53), respectively. So, despite medical advancements, Type D seems to have a relatively stable prognostic effect across these cohorts, justifying merging of all cohorts into one.

3.3. Different endpoint as a source of heterogeneity

The continuous Type D score as measured by the interaction of negative affectivity and social inhibition scales was associated with an increased risk of MACE (p = .001) and cardiac death/MI (p = .01) after adjustment for statistical covariates and the main trait effects of negative affectivity and social inhibition (Table 2). LVEF ≤ 50%, decreased physical fitness and no CABG at baseline were also independent predictors of MACE and cardiac death/MI. In contrast, Type D personality was not associated with non-cardiac causes of death (Table 2, last column). In fact, LVEF, CABG and PCI were also unrelated to this endpoint, and only increasing age and decreased physical fitness were significantly associated with an increased risk of non-cardiac death.

These findings were replicated using the categorical Type D approach based on the cutoff ≥10 on NA and SI scales. Only patients with Type D (NA ≥ 10 and SI ≥ 10) - but not those with NA or SI only - had an increased risk of MACE (Fig. 1). Decreased LVEF, poor fitness and no CABG at baseline were other independent predictors of MACE. Type D was also independently associated with increased risk of cardiac death/MI (OR = 2.49; 95%CI 1.55–3.99, p < .0001) but this was not the case for NA only (OR = 0.42; 95%CI 0.18–0.99, p = .048) or SI only (OR = 0.95; 95%CI 0.50–1.79, p = .86). However, the categorical Type D measure (OR = 1.23; 95%CI 0.57–2.69, p = .60), decreased LVEF, CABG and PCI did not predict non-cardiac cause of death. Only increasing age (OR = 1.06; 95%CI 1.02–1.10, p = .004) and decreased physical fitness (OR = 3.90; 95%CI 1.85–8.24, p < .00014) were significantly associated with this endpoint.

3.4. Age as a source of heterogeneity

We repeated the analysis for MACE in the four pre-specified age subgroups. There were 113 patients who were 70 years or older, 522 between 60 and 69, 569 between 50 and 59 and 299 younger than 50. In this age subgroup analysis, we used the traditional Type D *versus* non-Type D dichotomy in order to compare these findings with the initial

Table 2
Risk estimates for MACE, cardiac death/MI and non-cardiac death.*

	MACE (n = 295)		Cardiac death/MI (n = 116)		Non-cardiac death (n = 37)	
	OR [95% CI]	p	OR [95% CI]	p	OR [95% CI]	p
Clinical covariates						
Age	0.99 [0.98–1.01]	.26	1.00 [0.98–1.02]	.97	**1.06 [1.02–1.10]**	**.004**
Male sex	0.98 [0.65–1.49]	.94	1.62 [0.80–3.26]	.18	0.58 [0.24–1.40]	.23
Index MI at baseline	0.93 [0.68–1.28]	.66	0.93 [0.59–1.48]	.76	2.06 [0.94–4.52]	.071
Decreased LVEF (<50%)	**1.46 [1.07–1.98]**	**.015**	**2.27 [1.49–3.44]**	**<.0001**	0.96 [0.44–2.09]	.91
Poor exercise tolerance	**1.76 [1.33–2.32]**	**<.0001**	**1.95 [1.29–2.94]**	**.001**	**3.80 [1.80–8.03]**	**<.0001**
CABG at baseline	**0.40 [0.28–0.57]**	**<.0001**	**0.33 [0.19–0.55]**	**.0001**	0.81 [0.34–1.92]	.63
PCI at baseline	0.79 [0.57–1.11]	.18	**0.56 [0.34–0.92]**	**.02**	0.49 [0.19–1.28]	.15
Continuous Type D measures						
Negative affectivity (NA z score)	1.13 [0.98–1.30]	.093	1.02 [0.82–1.27]	.86	0.88 [0.59–1.31]	.53
Social inhibition (SI z score)	1.07 [0.92–1.23]	.39	1.21 [0.98–1.50]	.08	1.33 [0.93–1.90]	.12
NA x SI interaction (Type D)	**1.24 [1.09–1.39]**	**.001**	**1.25 [1.05–1.49]**	**.01**	1.19 [0.86–1.65]	.29

CABG = coronary artery bypass surgery; MACE = major adverse cardiac event; MI = myocardial infarction; NA = negative affectivity; PCI = percutaneous coronary intervention; SI = social inhibition.
[1]Left ventricular ejection fraction ≤50%.
[2]≤140/≤120 W for younger/older men; ≤100/≤80 W for younger/older women.
* Multivariable logistic regression models with all variables entered simultaneously. Bold: significant at p < .05 level

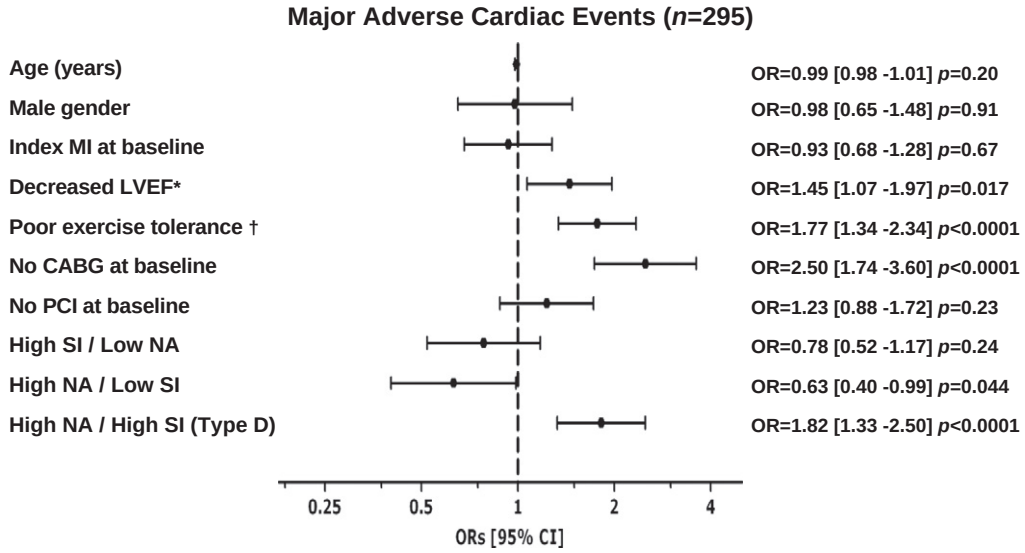

Fig. 1. Multivariable predictors of MACE, using the categorical Type D approach. Note: * Left ventricular ejection fraction ≤50%. † ≤140/≤120 W for younger/older men; ≤100/≤80 W for younger/older women. CABG = coronary artery bypass graft surgery; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NA = negative affectivity; PCI = percutaneous coronary intervention; SI = social inhibition.

Type D reports that also used this dichotomy [24–27]. For this purpose, patients with high NA/low SI, high SI/low NA, or low on both NA and SI were pooled in one non-Type D reference group. There was a dose–response relationship between Type D personality and incidence of adverse events, with the risk increasing with decreasing age (Fig. 2). In the *aged over 70* subgroup, Type D was not associated with MACE (p = .57), but in the younger age subgroups, Type D was predictive of MACE (*Aged 60–69,* p = .001; *Aged 50–59,* p < .0001; *Aged below 50,* p = .002). Multivariable analyses showed that not receiving CABG treatment was the only significant predictor of MACE in the oldest age group, while decreased LVEF, poor exercise tolerance, no CABG at baseline, and Type D personality were all independently associated with MACE in the middle-aged group (Table 3). Remarkably, Type D personality was the only significant predictor of MACE in the subgroup aged below 50 years (Table 3, last column).

4. Discussion

The current study aimed to examine the effects of two potential sources of heterogeneity affecting the association between Type D personality and adverse events in patients with CAD. Results indicated that both the choice of endpoint (i.e. cardiac mortality/MI vs. non-cardiac mortality) and the age distribution of the sample significantly impacted risk estimates of adverse events associated with Type D personality.

The selection of endpoints is very important in clinical trials and epidemiological studies [33]. The current study compared MACE with cardiac death/MI and non-cardiac death, with the latter comparison being of utmost importance. Although studying all-cause mortality has practical advantages (e.g., easy to assess, no interpretation biases), it can dilute the significance of risk factors whose mechanistic pathways affect disease-specific causes of death [17]. Studying cardiac death/MI brings higher sensitivity to the risk factor effect, and resistance to influence of random variations in other outcomes that are unlikely to be affected by the risk factor [17]. These factors may explain the currently observed differential effect of Type D personality on cardiac vs. non-cardiac death. The biological mechanistic pathways that have been associated with Type D personality are disease-specific and involve increased coronary plaque severity [34,35], higher macrophage activity [36], increased pro-inflammatory activation [37] and oxidative stress [38], endothelial dysfunction [39,40], increased daytime cortisol output [41], altered cardiovascular stress reactivity [42,43], and acute stunning of the myocardium in response to stress [44]. These findings support the biological plausibility of Type D as a cardiac risk marker, and indicate that the Type D-associated risk estimate, which is hypothesized to work through disease-specific pathways, may become diluted when examining all-cause mortality in a cardiac population. Accordingly, Type D was unrelated to non-cardiac death in the current sample of patients with CAD, which may partly explain the null findings in Type D studies that used all-cause mortality as an endpoint [10–13]. Depression also failed to predict all-cause mortality in the majority of negative Type D studies [11–13], suggesting that the choice of endpoint may be important for psychosocial factors in general.

The other pre-specified subgroup analysis concerned age as an effect modifier. Previous studies have shown that older patients already have a higher mortality risk compared to younger patients, due to myocardial ageing (i.e. cellular processes), more medical comorbidities, and decreased treatment choices [19–21]. The present findings show that Type D predicted MACE and cardiac death/MI in the *aged below 70* subgroup, but not in the patients *aged 70 or higher*. By analogy, a number

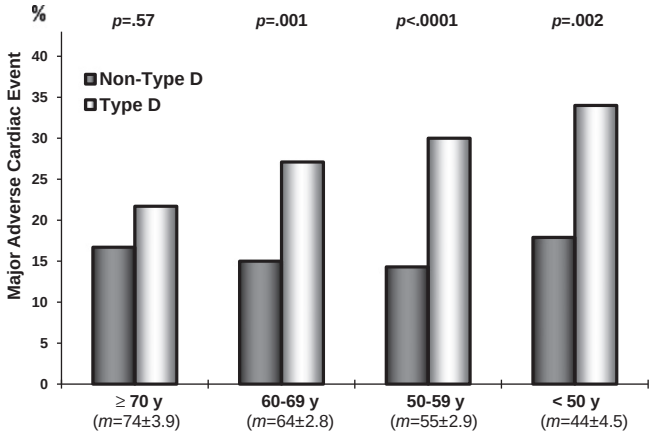

Fig. 2. Association of Type D versus non-Type D personality with MACE in 4 different age groups. Note: MI = myocardial infarction. M = mean.

Table 3
Risk estimates for MACE, stratified by older, middle-aged and younger age groups.*

	70 years or older (m = 74 ± 3.9 y) n = 113		Between 50 and 69 years (m = 59 ± 5.4 y) n = 1091		Below 50 years (m = 44 ± 4.5 y) n = 299	
	OR [95% CI]	p	OR [95% CI]	p	OR [95% CI]	p
Clinical covariates						
Decreased LVEF (<50%)	1.65 [0.55–4.99]	.38	**1.56 [1.09–2.25]**	**.016**	1.05 [0.55–2.03]	.88
Poor exercise tolerance	2.50 [0.71–8.81]	.16	**1.85 [1.33–2.56]**	<**.0001**	1.44 [0.79–2.65]	.24
No CABG at baseline	**4.24 [1.23–14.65]**	**.022**	**2.44 [1.66–3.58]**	<**.0001**	*1.93 [0.94–3.96]*	*.074*
No PCI at baseline	0.87 [0.25–2.95]	.82	1.34 [0.89–2.02]	.17	1.08 [0.55–2.11]	.83
Dichotomous Type D measure						
NA ≥ 10 and SI ≥ 10 (Type D)	1.43 [0.43–4.80]	.57	**2.20 [1.59–3.03]**	<**.0001**	**2.27 [1.31–3.95]**	**.004**

CABG = coronary artery bypass surgery; MACE = major adverse cardiac event; MI = myocardial infarction; NA = negative affectivity; PCI = percutaneous coronary intervention; SI = social inhibition. Bold = significant at p < .05 level; Italic = significant at trend level (p < .10)

* Multivariable logistic regression models with all variables entered simultaneously.

of negative Type D studies [11,12] included patients that were on average about 10 years older as compared to the patients that were included in the present analyses [24–27]. Studies that also used the 70 years of age breakdown in cardiac patients showed a) that mortality risks differed in the ≥70 group *versus* the younger group [45], and b) that, as was the case with Type D in the current study, depression predicted adverse events in younger but not in older patients [46]. Hence, it is possible that CAD patients with depression or Type D who die at an earlier age may be more vulnerable to stress-related cardiac events than those who survive to old age [15]. Moreover, research has repeatedly shown that younger patients have a different risk profile, clinical presentation, prognosis and experience more pronounced psychological and social effects [47,48]. Aging may be accompanied by a gradual cognitive decline, mostly with respect to memory and cognitive processing speed [49], as well as by changes in personality [50,51]. A recent study in patients with CAD, showed that Type D personality was associated with worse cognitive performance, independent of clinical measures of disease severity [52]. In patients with CAD, cognitive impairment has also been related to increased mortality risk [53]. Hence, accelerated cognitive decline, as a marker of advancing biological aging, could serve as one of the explanatory mechanisms linking Type D personality with increased mortality risk at relatively earlier ages [54]. Nonetheless, at later ages, medical comorbidities might play a more prominent role in explaining increased mortality than personality. Overall, these age group specific findings further corroborate the notion that age may moderate the risk estimates associated with psychosocial risk factors.

Our findings should be interpreted with appropriate caution because this is a re-analysis of 4 combined CAD cohorts. However, re-analyses are not uncommon when studying effect modifiers, and secondary analyses of clinical trials such as ENRICHD (e.g., [55,56]) have also addressed this issue. All patients were recruited from a cardiac rehabilitation program in a single university medical center, which may limit generalizability. Most patients were men with CAD and our findings may not generalize to women with CAD or to patients with other cardiac conditions. Future studies should include more women in order to examine sex differences in Type D related mortality, its predictors and its effect moderators. Finally, the use of different Type D measures is a limitation of this pooled data set. Strengths of this re-analysis include the relatively large number of events in the combined dataset, and the theory-based and predefined subgroup analyses.

To better understand the interactive networks of risk factors involved in CAD incidence and progression, a more subtle and sophisticated approach is required from future research. In addition to complicated network analyses, this involves the search for moderators revealing at what ages, or in what subgroups and for what outcomes risk factor associations hold [15]. Other moderator analyses that have been performed to date suggest moderator effects of disease severity [57], sex, and ethnicity [58] on mortality in CAD patients. Clinically, this is important as well. Taking sources of heterogeneity into consideration may be useful to improve effectiveness of personalized interventions aimed at reducing the risk for adverse health outcomes conferred by Type D [59,60].

In summary, our findings indicate that research should account for the circumstances under which risk factors, in this case Type D, but also other psychological risk factors [46], may have an adverse effect on cardiac outcomes. Type D consistently predicted adverse events in patients with MACE or cardiac death/MI while Type D personality had no effect on non-cardiac death or in older patients with CAD. Overall, these findings suggest that heterogeneity in study and sample characteristics may at least partly explain mixed findings in Type D research, and research on CAD needs to consider psychosocial factors whose mechanistic pathways are likely to affect the cardiovascular system.

Conflict of interest

No conflict of interest exists for any of the authors.

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References

[1] T.G. Briffa, M.S. Hobbs, A. Tonkin, F.M. Sanfilippo, S. Hickling, S.C. Ridout, et al., Population trends of recurrent coronary heart disease event rates remain high, Circ. Cardiovasc. Qual. Outcomes 4 (1) (2011) 107–113.
[2] J.H. Lichtman, E.S. Froelicher, J.A. Blumenthal, R.M. Carney, L.V. Doering, N. Frasure-Smith, et al., Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: systematic review and recommendations: a scientific statement from the American Heart Association, Circulation 129 (12) (2014) 1350–1369.
[3] A.M. Roest, E.J. Martens, P. de Jonge, J. Denollet, Anxiety and risk of incident coronary heart disease: a meta-analysis, J. Am. Coll. Cardiol. 56 (1) (2010) 38–46.
[4] A. Steptoe, G.J. Molloy, Personality and heart disease, Heart 93 (7) (2007) 783–784.
[5] M.E. Beutel, J. Wiltink, Y. Till, P.S. Wild, T. Munzel, F.M. Ojeda, et al., Type D personality as a cardiovascular risk marker in the general population: results from the Gutenberg health study, Psychother. Psychosom. 81 (2) (2012) 108–117.
[6] J. Denollet, A.A. Schiffer, V. Spek, A general propensity to psychological distress affects cardiovascular outcomes: evidence from research on the Type D (distressed) personality profile, Circ. Cardiovasc. Qual. Outcomes 3 (5) (2010) 546–557.
[7] G. Grande, M. Romppel, J. Barth, Association between Type D personality and prognosis in patients with cardiovascular diseases: a systematic review and meta-analysis, Ann. Behav. Med. 43 (3) (2012) 299–310.
[8] K.R. O'Dell, K.S. Masters, G.I. Spielmans, S.A. Maisto, Does Type D personality predict outcomes among patients with cardiovascular disease? A meta-analytic review, J. Psychosom. Res. 71 (4) (2011) 199–206.
[9] J. Reich, A. Schatzberg, Personality traits and medical outcome of cardiac illness, J. Psychiatr. Res. 44 (15) (2010) 1017–1020.
[10] N.L. Damen, H. Versteeg, E. Boersma, P.W. Serruys, R.J. van Geuns, J. Denollet, et al., Depression is independently associated with 7-year mortality in patients treated with percutaneous coronary intervention: results from the RESEARCH registry, Int. J. Cardiol. 167 (6) (2013) 2496–2501.

[11] A.J. Pelle, S.S. Pedersen, A.A. Schiffer, B. Szabo, J.W. Widdershoven, J. Denollet, Psychological distress and mortality in systolic heart failure, Circ. Heart Fail. 3 (2) (2010) 261–267.
[12] J.C. Coyne, T. Jaarsma, M.L. Luttik, E. van Sonderen, D.J. van Veldhuisen, R. Sanderman, Lack of prognostic value of Type D personality for mortality in a large sample of heart failure patients, Psychosom. Med. 73 (7) (2011) 557–562.
[13] G. Grande, M. Romppel, J.M. Vesper, R. Schubmann, H. Glaesmer, C. Herrmann-Lingen, Type D personality and all-cause mortality in cardiac patients–data from a German cohort study, Psychosom. Med. 73 (7) (2011) 548–556.
[14] J. Denollet, Interpersonal sensitivity, social inhibition, and Type D personality: how and when are they associated with health? Comment on Marin and Miller (2013), Psychol. Bull. 139 (5) (2013) 991–997.
[15] W.T. Boyce, M.B. Sokolowski, G.E. Robinson, Toward a new biology of social adversity, Proc. Natl. Acad. Sci. U. S. A. 109 (Suppl. 2) (2012) 17143–17148.
[16] J. Wittes, On looking at subgroups, Circulation 119 (7) (2009) 912–915.
[17] D.L. Mann, Heart Failure. A Companion to Braunwald's Heart Disease, Second edition Elsevier Saunders, Philadelphia, USA, 2010 570–593.
[18] J.D. Berry, D.M. Lloyd-Jones, D.B. Garside, R. Wang, P. Greenland, Social avoidance and long-term risk for cardiovascular disease death in healthy men: the Western Electric study, Ann. Epidemiol. 17 (8) (2007) 591–596.
[19] H. Shih, B. Lee, R.J. Lee, A.J. Boyle, The aging heart and post-infarction left ventricular remodeling, J. Am. Coll. Cardiol. 57 (1) (2011) 9–17.
[20] E.L. Tay, M. Chan, V. Tan, L.L. Sim, H.C. Tan, Y.T. Cheng, Impact of combination evidence-based medical therapy on mortality following myocardial infarction in elderly patients, Am. J. Geriatr. Cardiol. 17 (1) (2008) 21–26.
[21] S. Barlera, L. Tavazzi, M.G. Franzosi, R. Marchioli, E. Raimondi, S. Masson, et al., Predictors of mortality in 6975 patients with chronic heart failure in the Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico-Heart Failure trial: proposal for a nomogram, Circ. Heart Fail. 6 (1) (2013) 31–39.
[22] J. Denollet, F.B. Tekle, P.H. van der Voort, M. Alings, K.C. van den Broek, Age-related differences in the effect of psychological distress on mortality: Type D personality in younger versus older patients with cardiac arrhythmias, Biomed. Res. Int. 2013 (2013) 246035.
[23] K.P. Alexander, L.K. Newby, C.P. Cannon, P.W. Armstrong, W.B. Gibler, M.W. Rich, et al., Acute coronary care in the elderly, part I: non-ST-segment-elevation acute coronary syndromes: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: in collaboration with the Society of Geriatric Cardiology, Circulation 115 (19) (2007) 2549–2569.
[24] J. Denollet, S.U. Sys, N. Stroobant, H. Rombouts, T.C. Gillebert, D.L. Brutsaert, Personality as independent predictor of long-term mortality in patients with coronary heart disease, Lancet 347 (8999) (1996) 417–421.
[25] J. Denollet, J. Vaes, D.L. Brutsaert, Inadequate response to treatment in coronary heart disease: adverse effects of Type D personality and younger age on 5-year prognosis and quality of life, Circulation 102 (6) (2000) 630–635.
[26] J. Denollet, S.S. Pedersen, C.J. Vrints, V.M. Conraads, Usefulness of Type D personality in predicting five-year cardiac events above and beyond concurrent symptoms of stress in patients with coronary heart disease, Am. J. Cardiol. 97 (7) (2006) 970–973.
[27] J. Denollet, S.S. Pedersen, C.J. Vrints, V.M. Conraads, Predictive value of social inhibition and negative affectivity for cardiovascular events and mortality in patients with coronary artery disease: the Type D personality construct, Psychosom. Med. 75 (9) (2013) 873–881.
[28] J. Denollet, Personality and coronary heart disease: the Type D scale-16 (DS16), Ann. Behav. Med. 20 (3) (1998) 209–215.
[29] J. Denollet, DS14: standard assessment of negative affectivity, social inhibition, and Type D personality, Psychosom. Med. 67 (1) (2005) 89–97.
[30] T.W. Smith, Toward a more systematic, cumulative, and applicable science of personality and health: lessons from Type D personality, Psychosom. Med. 73 (7) (2011) 528–532.
[31] J.S. Gottdiener, R.L. McClelland, R. Marshall, L. Shemanski, C.D. Furberg, D.W. Kitzman, et al., Outcome of congestive heart failure in elderly persons: influence of left ventricular systolic function - the cardiovascular health study, Ann. Intern. Med. 137 (8) (2002) 631–639.
[32] J.A. Laukkanen, T.H. Makikallio, R. Rauramaa, V. Kiviniemi, K. Ronkainen, S. Kurl, Cardiorespiratory fitness is related to the risk of sudden cardiac death: a population-based follow-up study, J. Am. Coll. Cardiol. 56 (18) (2010) 1476–1483.
[33] G.F. Borm, S. Teerenstra, G.A. Zielhuis, Objective and perspective determine the choice of composite endpoint, J. Clin. Epidemiol. 61 (2) (2008) 99–101.
[34] A. Compare, P.M. Mommersteeg, F. Faletra, E. Grossi, E. Pasotti, T. Moccetti, et al., Personality traits, cardiac risk factors, and their association with presence and severity of coronary artery plaque in people with no history of cardiovascular disease, J. Cardiovasc. Med. (Hagerstown) 15 (5) (2014) 423–430.
[35] Y. Wang, Z. Zhao, X. Gao, L. Li, G. Liu, W. Chen, et al., Type D personality and coronary plaque vulnerability in patients with coronary artery disease: an optical coherence tomography study, Psychosom. Med. (2016).
[36] C. Zuccarella-Hackl, R. von Kanel, L. Thomas, P. Kuebler, J.P. Schmid, H.P. Mattle, et al., Higher macrophage superoxide anion production in coronary artery disease (CAD) patients with Type D personality, Psychoneuroendocrinology 68 (2016) 186–193.
[37] J. Denollet, A.A. Schiffer, M. Kwaijtaal, H. Hooijkaas, E.H. Hendriks, J.W. Widdershoven, et al., Usefulness of Type D personality and kidney dysfunction as predictors of interpatient variability in inflammatory activation in chronic heart failure, Am. J. Cardiol. 103 (3) (2009) 399–404.
[38] N. Kupper, Y. Gidron, J. Winter, J. Denollet, Association between Type D personality, depression, and oxidative stress in patients with chronic heart failure, Psychosom. Med. 71 (9) (2009) 973–980.
[39] F. Khorvash, M. Rahimi, R. Bagherian-Sararoudi, S.A. Mousavi, A. Ebneshahidi, A. Amirpour, et al., Evaluation of intima media thickness of carotid arteries in 40–60 years old persons with Type D personality and its comparison with normal ones, Int. J. Prev. Med. 4 (Suppl. 2) (2013) S250–S255.
[40] E. Van Craenenbroeck, J. Dcnollet, P. Beckers, N. Possemiers, K. Wuyts, V. Hoymans, et al., Reduction of circulating endothelial progenitor cells in chronic heart failure patients as a function of Type D personality, Acta Cardiol. 64 (1) (2009) 136–137.
[41] G.J. Molloy, L. Perkins-Porras, P.C. Strike, A. Steptoe, Type D personality and cortisol in survivors of acute coronary syndrome, Psychosom. Med. 70 (8) (2008) 863–868.
[42] N. Kupper, J. Denollet, J. Widdershoven, W.J. Kop, Type D personality is associated with low cardiovascular reactivity to acute mental stress in heart failure patients, Int. J. Psychophysiol. 90 (1) (2013) 44–49.
[43] A. Bibbey, D. Carroll, A.T. Ginty, A.C. Phillips, Cardiovascular and cortisol reactions to acute psychological stress under conditions of high versus low social evaluative threat: associations with the Type D personality construct, Psychosom. Med. 77 (5) (2015) 599–608.
[44] A. Compare, R. Bigi, P.S. Orrego, R. Proietti, E. Grossi, A. Steptoe, Type D personality is associated with the development of stress cardiomyopathy following emotional triggers, Ann. Behav. Med. 45 (3) (2013) 299–307.
[45] H.M. van Loo, E.R. van den Heuvel, R.A. Schoevers, M. Anselmino, R.M. Carney, J. Denollet, et al., Sex dependent risk factors for mortality after myocardial infarction: individual patient data meta-analysis, BMC Med. 12 (1) (2014) 1–9.
[46] J. Denollet, K.E. Freedland, R.M. Carney, P. de Jonge, A.M. Roest, Cognitive-affective symptoms of depression after myocardial infarction: different prognostic importance across age groups, Psychosom. Med. 75 (7) (2013) 701–708.
[47] P.J. Morillas, A. Cabadés, V. Bertomeu, I. Echanove, F. Colomina, J. Cebrián, et al., Acute myocardial infarction in patients under 45 years, Rev. Esp. Cardiol. (Engl. Ed.) 55 (11) (2002) 1124–1131.
[48] M. Egred, G. Viswanathan, G.K. Davis, Myocardial infarction in young adults, Postgrad. Med. J. 81 (962) (2005) 741–745.
[49] Handbook of Cognitive Aging: Interdisciplinary Perspectives, SAGE Publications, Inc., Thousand Oaks, California, 2008 (Available from: http://sk.sagepub.com/reference/hdbk_cognativeaging).
[50] J. Wagner, N. Ram, J. Smith, D. Gerstorf, Personality trait development at the end of life: antecedents and correlates of mean-level trajectories, J. Pers. Soc. Psychol. 111 (3) (2016) 411–429.
[51] R.G. Curtis, T.D. Windsor, A. Soubelet, The relationship between Big-5 personality traits and cognitive ability in older adults - a review, Neuropsychol. Dev. Cogn. B Aging Neuropsychol. Cogn. 22 (1) (2015) 42–71.
[52] J. Burkauskas, J. Brozaitiene, A. Bunevicius, J. Neverauskas, V. Zaliunaite, R. Bunevicius, Association of depression, anxiety, and Type D personality with cognitive function in patients with coronary artery disease, Cogn. Behav. Neurol. 29 (2) (2016) 91–99.
[53] L.P. Fried, R.A. Kronmal, A.B. Newman, et al., Risk factors for 5-year mortality in older adults: the cardiovascular health study, JAMA 279 (8) (1998) 585–592.
[54] J. Denollet, C.J. Vrints, V.M. Conraads, Comparing Type D personality and older age as correlates of tumor necrosis factor-alpha dysregulation in chronic heart failure, Brain Behav. Immun. 22 (5) (2008) 736–743.
[55] A.M. Roest, R.M. Carney, K.E. Freedland, E.J. Martens, J. Denollet, P. de Jonge, Changes in cognitive versus somatic symptoms of depression and event-free survival following acute myocardial infarction in the Enhancing Recovery In Coronary Heart Disease (ENRICHD) study, J. Affect. Disord. 149 (1–3) (2013) 335–341.
[56] R.M. Carney, J.A. Blumenthal, K.E. Freedland, M. Youngblood, R.C. Veith, M.M. Burg, et al., Depression and late mortality after myocardial infarction in the enhancing recovery in coronary heart disease (ENRICHD) study, Psychosom. Med. 66 (4) (2004) 466–474.
[57] T. Meyer, U. Buss, C. Herrmann-Lingen, Role of cardiac disease severity in the predictive value of anxiety for all-cause mortality, Psychosom. Med. 72 (1) (2010) 9–15.
[58] R.D. Keeley, M. Driscoll, A moderator-mediator analysis of coronary heart disease mortality, J. Psychosom. Res. 69 (6) (2010) 549–554.
[59] J. Denollet, N. Kupper, Stress and the heart: the role of Type D personality in personalized care, Eur. Heart J. 36 (28) (2015) 1783–1785.
[60] C. Herrmann-Lingen, M.E. Beutel, A. Bosbach, et al., For the SPIRR-CAD Study Group. A stepwise psychotherapy intervention for reducing risk in coronary artery disease (SPIRR-CAD) – results of an observer-blinded, multicenter, randomized trial in depressed patients with CAD, Psychosom. Med. 78 (6) (2016) 704–715.